# The prognosis of mid-range ejection fraction heart failure: a systematic review and meta-analysis

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## Abstract

**Aims** Mid-range ejection fraction is a new entity of heart failure (HF) with undetermined prognosis till now. In our systematic review and meta-analysis, we assess the mortality and hospitalization rates in mid-range ejection fraction HF (HFmrEF) and compare them with those of reduced ejection fraction heart failure (HFrEF) and preserved ejection fraction HF (HFpEF).

**Methods and results** We conducted our search in March 2018 in the following databases for relevant articles: PubMed, CENTRAL, Google Scholar, Web of Science, Scopus, NYAM, SIEGLE, GHL, VHL, and POPLINE. Our primary endpoint was assessing all-cause mortality and all-cause hospital re-admission rates in HFmrEF in comparison with HFrEF and HFpEF. Secondary endpoints were the possible causes of death and hospital re-admission. Twenty-five articles were included in our meta-analysis with a total of 606 762 adult cardiac patients. Our meta-analysis showed that HFmrEF had a lower rate of all-cause death than had HFrEF [relative risk (RR), 0.9; 95% confidence interval (CI), 0.85–0.94]. HFpEF showed a higher rate of cardiac mortality than did HFmrEF (RR, 1.09; 95% CI, 1.02–1.16). Also, HFrEF had a higher rate of non-cardiac mortality than had HFmrEF (RR, 1.31; 95% CI, 1.22–1.41).

**Conclusions** We detected a significant difference between HFrEF and HFmrEF regarding all-cause death, and non-cardiac death, while HFpEF differed significantly from HFmrEF regarding cardiac death.

Keywords Heart failure with mid-range ejection fraction; Mortality; Hospitalization; Meta-analysis

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## Introduction

Left ventricular ejection fraction (LVEF) has long been used in the stratification of patients with HF, although it is not an ideal parameter owing to its relative subjectivity. The lack of evidence supporting the use of other parameters such as myocardial deformation imaging made LVEF widely accepted for stratifying HF patients.<sup>1</sup>

Considering LVEF, there are three types of heart failure (HF); the largest is the reduced ejection fraction (HFrEF) (EF < 40%), which is widely distributed, and the smallest is the preserved ejection fraction (HFpEF) (EF > 50%).<sup>2</sup> Although HFpEF was considered in the literature only two decades ago, it proved that almost half of HF patients fall in this category with an expected rise in the future.<sup>3</sup> Between these two types, there is the mid-range ejection fraction

(HFmrEF) (EF 40–49%), which is considered as a grey zone according to the European Society of Cardiology guidelines.<sup>2,4</sup>

Although few studies described HFmrEF prevalence in comparison with that of other HF types, HFmrEF proved to have intermediate clinical picture, haemodynamics, laboratory findings, and echocardiographic data between the other two types.<sup>1,5–7</sup>

In 2017 and depending on a registry report, the mortality rates of HFmrEF, HFrEF, and HFpEF were reported<sup>8</sup>; however, a stronger evidence is needed to estimate the rate difference.

In our meta-analysis, we measured all-cause mortality, cardiac mortality, non-cardiac mortality, all-cause hospitalization, and HF-related hospitalization in HFmrEF in comparison with HFrEF and HFpEF to better understand the differences between the three subgroups and to determine the features of HFmrEF.

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# **Methods**

The study is written according to the guidelines and recommendations in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.<sup>9</sup> No published protocol for this systematic review and meta-analysis exists.

#### Literature search strategy

We conducted a systematic search in PubMed, CENTRAL, Google Scholar, Web of Science, Scopus, NYAM, SIEGLE, GHL, VHL, and POPLINE using the terms *mid-range ejection fraction heart failure, mid-range ejection fraction heart failure, borderline ejection fraction heart failure, HFmrEF, prognosis, mortality, death,* and *re-admission.* We conducted this search in December 2017, and it was updated in March 2018.

## **Study selection**

Studies were eligible if (i) they aimed at defining the prognosis of HFmrEF in terms of mortality and hospitalization, (ii) they included patients (adult men or women) aged >18 years old with no restriction to the date of publication, and (iii) the studies defined HF subtypes according to the European Society of Cardiology guidelines (HFrEF as <40%, HFmrEF as 40–49%, and HFpEF as  $\geq$ 50%).<sup>2,4</sup> We did not include studies not restricting to this guideline for fear of data overlap between the HF subtypes.Reviews, comments, duplicated publications, non-English articles, articles with unreliable data extraction, and pooling analyses of original studies were excluded. After including the eligible articles, we manually searched the reference lists of these studies for relevant articles.

#### Data extraction and quality assessment

The following data were extracted: (i) study characteristics like study title, year of publication, study design, country of study, inclusion criteria of the patients, total sample size, number of patients in each category of HF, their ages, and their gender male percentage; and (ii) criteria of the study outcomes like all-cause mortality, cardiac mortality, noncardiac mortality, all-cause hospitalization, and HF-related hospitalization.

The methodological quality of included studies was appraised using National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.<sup>10</sup> The score consists of 14 questions covering the assessment of the study methodology. A study was given one or zero points according to its fulfilment of the

## **Statistical analysis**

The study measures included all-cause mortality, cardiac mortality, non-cardiac mortality, all-cause hospitalization, and HFrelated hospitalization.

All statistical analyses were performed with the REVMAN software (version 5.3; Cochrane Collaboration, Oxford, UK). The Mantel–Haenszel method was used to calculate estimates, confidence intervals (CIs), and *P* values. Statistical heterogeneity was tested with the  $I^2$  statistic, with  $I^2 \leq 50\%$  indicating no significant heterogeneity.<sup>11</sup> In case of significant heterogeneity, a random effect model was used, while a fixed effect model was used in case of no significant heterogeneity. Relative risk (RR) was calculated from raw published study data, and all outcomes were reported with a 95% CI. For the  $\chi^2$  test, a *P* value < 0.05 was considered statistically significant.

## Results

## Search results

As shown in *Figure 1*, we identified 299 records in the preliminary search. After scanning the titles or abstracts and removing the duplicates, we excluded 238 articles. The remaining 61 publications underwent full-text screening, of which 42 failed to meet the inclusion criteria and were removed. On data extraction, 23 articles were excluded. On manual searching of the reference lists of the remaining 19 articles, we found another six articles to include. Finally, 25 articles were included in the final data analysis.<sup>3,8,12–34</sup>

#### Study characteristics

As shown in *Table 1*, the set of eligible studies consists of 10 prospective cohort studies and 15 retrospective studies with a total of 606 762 patients. The included studies were published from 2001 to 2018. The period of follow-up ranged from 1 month to 5 years, and the most common adjusted variables were age and sex. Regarding the quality of the studies, the NIH scores ranged from 9 to 13 with a mean of 11.2, suggesting the presence of high methodological quality.

#### **All-cause death**

As shown in *Figure 2*, HFmrEF had a significantly lower allcause death rate than had HFrEF (RR, 0.9; 95% CI, 0.85–



Figure 1 Flow chart showing the number of included papers after literature search, title/abstract screening, full text screening, data extraction, and final data analysis.

0.94; P < 0.001). On the other hand, there was no significant difference between HFpEF and HFmrEF (RR, 0.98; 95% Cl, 0.86–1.12; P = 0.82). Both analyses detected high levels of heterogeneity ( $I^2 = 84\%$  and  $I^2 = 98\%$ ).

#### Cardiac and non-cardiac mortality rates

As shown in *Figure 3*, the pooled analyses of the cardiac mortality results showed no significant difference between HFrEF and HFmrEF (RR, 0.89; 95% CI, 0.69–1.15; P = 0.38), but HFpEF had a significantly higher cardiac mortality rate than had HFmrEF (RR, 1.09; 95% CI, 1.02–1.16; P = 0.001). The two pooled analyses detected low levels of heterogeneity ( $I^2 = 0\%$  and  $I^2 = 46\%$ ).

Regarding the non-cardiac mortality results, HFrEF had a significantly higher rate than had HFmrEF (RR, 1.31; 95% CI, 1.22–1.41; P < 0.001), while there was no significant difference between HFpEF and HFmrEF (RR, 0.91; 95% CI, 0.75–1.09; P = 0.3). The analyses showed low and high levels of heterogeneity ( $I^2 = 46\%$  and  $I^2 = 57\%$ ).

#### All-cause and HF-related hospitalization

As shown in *Figure 4*, the pooled analyses of all-cause hospitalization showed no significant difference between HFrEF and HFmrEF or between HFpEF and HFmrEF (RR, 0.91; 95% CI, 0.18–4.59; P = 0.9; and RR, 0.95; 95% CI, 0.84–1.07; P = 0.38, respectively). Both analyses detected high levels of heterogeneity ( $I^2 = 100\%$  and  $I^2 = 62\%$ ).

Regarding HF-related hospitalization, the pooled analyses showed also no significant differences between HFrEF and

HFmrEF or between HFpEF and HFmrEF (RR, 0.92; 95% CI, 0.84–1.01; P = 0.08; and RR, 1.05; 95% CI, 0.83–1.33; P = 0.69, respectively). Both analyses had high levels of heterogeneity ( $l^2 = 85\%$  and  $l^2 = 98\%$ ).

## Discussion

For a decade now, it has been uncertain as to whether HFmrEF should be considered as a separate clinical entity of HF and subsequently having different prognosis and treatment from HFpEF and HFrEF or not; so, in our study, we measured the mortality rates and hospital re-admission rates in the different types as a measure of this difference.

Moher *et al.*<sup>9</sup> and Gomez-Otero *et al.*<sup>12</sup> considered HFmrEF as part of HFrEF owing to its high prevalence of ischaemic heart disease and its response to N terminal pro-brain natriuretic peptide-guided therapy. On the other hand, Margolis *et al.*<sup>13</sup> and Coles *et al.*<sup>14</sup> considered HFmrEF as a separate clinical entity with intermediate features between HFrEF and HFpEF.<sup>13,14</sup>

Some studies suggested that HFmrEF represents a transitional status or an overlap zone between HFpEF and HFrEF, rather than an independent entity of HF, and another study showed that HFmrEF constitutes intermediate features between both HFpEF and HFrEF, with more similarities towards HFpEF than to HFrEF.<sup>35</sup>

Morbidity and mortality rates proved to be similar in HFpEF and HFrEF<sup>36</sup>; however, there are not enough studies to measure them in HFmrEF. On the other hand, there are many studies discussing all-cause mortality, HF-related

				Total		HFrEF			HFmrEF			НЕРЕЕ	
Study	Publication year	Patients' country	Design	sample size	Number	Age (years)	% men	Number	Age (years)	% men	Number	Age (years)	% men
Lam et al.	2018	New Zealand and Singapore	Prospective cohort	2039	1209	62.1 ± 13.2	83	256	65.8 ± 12.7	69	574	71.5 ± 11.8	52
Hamatani <i>et al.</i> Guisado-Espartero et al	2018 2018	Japan Spain	Retrospective cohort Prospective cohort	1792 2735	860 808	— 79 (72–84)	62	318 281	— 80 (74–84)	28	614 1664	— 81 (76–86)	37
Vedin <i>et al</i> . Shah <i>et al</i>	2017 2017	Sweden	Retrospective cohort Retrospective cohort	42 789 39 982	23 805 18 398	— 79 (73–85)	70 59	9225 3785	— 81 (74–86)	64 49	9957 18 299	— 82 (75 <u>–</u> 87)	45 33
Rickenbacher <i>et al.</i>	2017	Switzerland	Retrospective cohort	622	402	$75.5 \pm 7.5$	67	108	79 ± 6.8	20.4	112	$80.2 \pm 7.1$	92 92 92
Pascual-Figal et al.	2017	Spain	Retrospective cohort	3446	2351	$64.4 \pm 12.3$	76.8	460	$66.7 \pm 12.1$	73	635	72.1 ± 12.2	42.8
Margolis <i>et al</i> .	2017	Israel	Prospective cohort	2243	215	$67 \pm 15$	78	858	62 ± 13	79	1013	$60 \pm 12$	81
Choi <i>et al</i> .	2018	Korea	Prospective cohort	5625	3182			875			1357		
Koh <i>et al</i> .	2017	Sweden	Retrospective cohort	42 061	23 402	72 ± 12	71	9019	74 ± 12	60	9640	77 ± 11	45
Gomez-Otero et al.	2017	Spain	Retrospective cohort	1420	583	$68.2 \pm 12.8$	76.7	227	72.5 ± 11.1	67	610	75 ± 10.7	46.7
Farré <i>et al</i> .	2017	Spain	Prospective cohort	3580	2232	$66.2 \pm 12.5$	75.7	504	$68.1 \pm 12.9$	66.9	844	73.5 ± 11.4	44
Delepaul <i>et al.</i>	2017	France	Prospective cohort	482	258	$66 \pm 12$	72	115	$69 \pm 13$	72	109	71 ± 12	55
Chioncel <i>et al</i> .	2017	22 countries	Prospective cohort	9134	5460	$64 \pm 12.6$	78	2212	$64.2 \pm 14.2$	68.5	1462	$68.6 \pm 13.7$	52
Bonsu <i>et al.</i>	2017	Ghana	Prospective cohort	1488	354	$58.9 \pm 14.2$	48.1	265	$60.4 \pm 12.7$	50.2	878	$60.8 \pm 14.6$	43.3
Bhambhani <i>et al</i> .	2017	USA	Prospective cohort	28 820	1084	70 ± 10	64	200	72 ± 8	52	811	71 ± 9	41
Coles et al.	2015	USA	Retrospective cohort	4025	940	71.4	60	364	74.4	45.1	1476	75.7	33
Coles et al.	2014	USA	Retrospective cohort	3604	1479	73.7 ± 12.8	56.5	346	$76.1 \pm 11.4$	45.4	1779	$76.5 \pm 11.9$	33.4
Cheng et al.	2014	USA	Retrospective cohort	40 239	15 716	79 (72–85)	60	5626	81 (74–86)	49.5	18 897	82 (75–87)	32.7
Tsuji <i>et al</i> .	2017	Japan	Retrospective cohort	3480	730	$66.9 \pm 12.7$	76.7	596	$69.0 \pm 11.6$	71.8	2154	$71.7 \pm 10.9$	60.8
Steinberg et al.	2012	USA	Retrospective cohort	110 621	55 083	70 (58–80)	64	15 184	76 (65–84)	53	40 453	78 (67–85)	37
Toma <i>et al</i> .	2014	398 centres	Retrospective cohort	5687	4474	64 (54–73)	71.4	674	73 (64–81)	58.9	539	76 (66–82)	41.6
		across the											
Kanoor at al	2016	LISA	Batrospactive cohort	90 875	18 950	60 6 + 11 7	63 7	17 810	74.4 + 13.3	51 1	38 056	75 0 + 13 1	21.0
löfman at al	2012	Sweden	Retrospective conort	10 230	12 607	67 (59-76)	1.00	2087	71 (67-79)	77 5	3008	75 (65-87)	, r
Tsutsui <i>et al.</i>	2001	Japan	Prospective cohort	172	61	$67 \pm 14$	71	38	6 7 69	61	73	$69 \pm 16$	49
Numbers are expres	sed as mean	± SD or median	(inter-quartile range).										

Prognosis of HFmrEF

-	HFm	rEF	HFr	EF		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bhambhani 2017	63	200	312	1084	3.0%	1.09 [0.87, 1.37]	
Bonsu 2017	89	265	119	354	3.0%	1.00 [0.80, 1.25]	
Cheng 2014	1974	5626	5893	15716	7.5%	0.94 [0.90, 0.97]	-
Chioncel 2017	168	2212	480	5460	4.1%	0.86 [0.73, 1.02]	
Choi 2017	171	875	694	3182	4.6%	0.90 [0.77, 1.04]	
Coles 2014	242	346	1050	14/9	6.7%	0.99 [0.91, 1.06]	
Coles 2015	157	304	4/4	940	5.0%	0.86 [0.75, 0.98]	
Espartero 2017	10	291	226	258	2.5%	0.59 [0.30, 1.14]	I
Espanelo 2017 Farré 2017	221	504	1023	2232	5.7%	0.96 (0.86 1.07)	·
Gomez-Otero 2016	55	227	116	583	2.2%	1.22 [0.92, 1.61]	
Hamatani 2017	60	318	178	860	2.5%	0.91 [0.70, 1.19]	
Kapoor 2016	333	12819	1566	48950	5.5%	0.81 [0.72, 0.91]	
Koh 2017	2512	9019	6706	23402	7.6%	0.97 [0.93, 1.01]	
Lam 2018	30	256	233	1209	1.6%	0.61 [0.43, 0.87]	•
Löfman 2017	163	2087	1689	12607	4.5%	0.58 [0.50, 0.68]	
Margolis 2017	18	858	27	215	0.7%	0.17 [0.09, 0.30]	•
Pascual-Figal 2017	128	460	776	2351	4.4%	0.84 [0.72, 0.99]	
Rickenbacher 2017 Shoh 2017	2497	108	12047	402	4.3%	1.14 [0.97, 1.34]	
Steinberg 2012	248/	3285	1.497	55092	7.8%	0.85 (0.76, 0.06)	[
Toma 2013	349	674	166	4474	1 1 96	0.03 [0.76, 0.96]	
Tsuji 2017	41	596	57	730	1.4%	0.88 [0.60, 1.30]	
Tsutsui 2001	8	38	17	73	0.4%	0.90 [0.43, 1.90]	<→
Vedin 2017	3471	9225	9234	23805	7.7%	0.97 [0.94, 1.00]	-
Total (95% CI)		65942		224655	100.0%	0.90 [0.85, 0.94]	◆
Total events	12899		46637				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi	<sup>2</sup> = 149.2	25, df = 24	(P < 0.00	0001); I² =	= 84%	0.7 0.85 1 1.2
Test for overall effect:	Z = 4.25 (	P < 0.00	01)				HFmrEF HFrEF
	HEm	rFF	HEn	FF		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Testesi 0004	0	20	7	61	1 4 96	1 02 10 72 4 661	
	× *	.58			1 1 1 20	103111// 41131	
Delenaul 2001	8	38 115	10	109	1.4%	0.95 [0.72, 4.05]	
Delepaul 2007 Margolis 2017	8 10 18	38 115 858	10 13	109	1.7%	0.95 [0.41, 2.19]	
Delepaul 2001 Margolis 2017	8 10 18 23	38 115 858 674	10 13 23	109 1013	1.7%	1.63 [0.72, 4.65] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41]	
Delepaul 2001 Margolis 2017 Toma 2013	8 10 18 23 20	38 115 858 674 256	10 13 23	109 1013 539	1.7% 2.0% 2.6%	1.63 [0.72, 4.63] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.67, 1.25]	
Delepaul 2001 Margolis 2017 Toma 2013 Lam 2018 Touii 2017	8 10 18 23 30	38 115 858 674 256	10 13 23 80	109 1013 539 574	1.7% 2.0% 2.6% 3.4%	1.63 [0.72, 4.63] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25]	
Delepaul 2007 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017	8 10 18 23 30 41	38 115 858 674 256 596	10 13 23 80 97	109 1013 539 574 2057	1.7% 2.0% 2.6% 3.4% 3.6%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 4.00 [0.02, 4.42]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017	8 10 18 23 30 41 60	38 115 858 674 256 596 318	10 13 23 80 97 106	109 1013 539 574 2057 614	1.7% 2.0% 2.6% 3.4% 3.6% 4.0%	0.95 [0.42, 4.03] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016	8 10 18 23 30 41 60 55	38 115 858 674 256 596 318 227	10 13 23 80 97 106 118	109 1013 539 574 2057 614 610	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0%	0.95 [0.42, 4.63] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017	8 10 18 23 30 41 60 55 56	38 115 858 674 256 596 318 227 281	10 13 23 80 97 106 118 366	109 1013 539 574 2057 614 610 1664	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017	8 10 18 23 30 41 60 55 56 168	38 115 858 674 256 596 318 227 281 2212	10 13 23 80 97 106 118 366 92	109 1013 539 574 2057 614 610 1664 1462	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.1% 4.2%	1.83 (0.72, 4.83) 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017	8 10 18 23 30 41 60 55 56 168 63	38 115 858 674 256 596 318 227 281 2212 200	10 13 23 80 97 106 118 366 92 231	109 1013 539 574 2057 614 610 1664 1462 811	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.1% 4.2% 4.2%	1.83 (0.72, 4.83) 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017	8 10 18 23 30 41 60 55 56 168 63 89	38 115 858 674 256 596 318 227 281 2212 200 265	10 13 23 80 97 106 118 366 92 231 264	109 1013 539 574 2057 614 610 1664 1462 811 878	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.1% 4.2% 4.2% 4.4%	1.83 (0.72, 4.83) 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017	8 10 18 23 30 41 60 55 56 168 63 89 128	38 115 858 674 256 596 318 227 281 2212 200 265 460	10 13 23 80 97 106 118 366 92 231 264 178	109 1013 539 574 2057 614 610 1664 1462 811 878 635	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017	8 10 18 23 30 41 60 55 56 168 63 89 128 163	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087	10 13 23 80 97 106 118 366 92 231 264 178 313	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4% 4.4%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17]	
Delepaul 2001 Delepaul 2007 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017	8 10 18 23 30 41 60 55 56 61 68 63 89 128 163 70	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108	10 13 23 80 97 106 118 366 92 231 264 178 313 83	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112	1.4% 1.7% 2.0% 2.6% 3.4% 3.6% 4.0% 4.2% 4.2% 4.2% 4.4% 4.4% 4.5%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.26] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04]	
Delepaul 2001 Delepaul 2007 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bhambhani 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 70 171	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357	1.4% 2.0% 2.6% 3.4% 3.6% 4.0% 4.2% 4.2% 4.4% 4.4% 4.4% 4.4% 4.5%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 70 171 157	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476	1.4% 2.6% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4% 4.4% 4.4% 4.5% 4.6%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18]	
Delepaul 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015 Kapoor 2016	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 8085 364 12819	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142	109 1013 539 574 2057 614 1664 1466 1664 1465 811 878 635 3908 112 1357 1476 38056	1.4% 1.7% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4% 4.4% 4.4% 4.5% 4.5% 4.5% 4.6%	1.83 (0.72, 4.83) 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.18] 0.87 [0.77, 0.98]	
Tsuisui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Choi 2015 Kapoor 2016 Steinbero 2012	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 349	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056	1.7% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.4% 4.4% 4.4% 4.4% 4.5% 4.5% 4.6% 4.5% 4.7%	1.83 [0.72, 4.03] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04]	
Tsuisui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 349 221	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184 504	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009 444	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40354 884	1.7% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.2% 4.4% 4.4% 4.4% 4.5% 4.5% 4.6% 4.6% 4.7% 4.7%	0.95 [0.42, 4.03] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.93 [0.74, 0.94]	
Tsuisui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Banmbhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017 Coles 2014	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 349 221 242	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184 504	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009 444 1227	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40354 844 1770	1.7% 2.0% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4% 4.2% 4.4% 4.5% 4.5% 4.5% 4.6% 4.7% 4.7% 4.7%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.26] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.83 [0.74, 0.94] 1.01 [0.94, 1.40]	
Tsuisui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bhambhani 2017 Bhambhani 2017 Rickenbacher 2017 Choi 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017 Coles 2014 Kob 2007	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 349 221 242 2512	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184 504 346 9010	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009 444 1227 3190	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40354 844 1779 9640	1.4% 1.7% 2.6% 3.4% 3.6% 4.0% 4.0% 4.0% 4.2% 4.4% 4.4% 4.4% 4.5% 4.5% 4.5% 4.6% 4.7% 4.7% 4.8% 4.7%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.83 [0.74, 0.94] 1.01 [0.94, 1.09] 0.84 [0.91, 1.09]	
Delepaul 2001 Delepaul 2007 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bhambhani 2017 Bhambhani 2017 Pascual-Figal 2017 Löfman 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017 Coles 2014 Koh 2017	8 10 18 230 41 60 55 56 168 63 89 128 163 89 128 163 30 70 171 157 333 349 221 242 2512	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184 504 346 9019 5626	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009 444 1227 3180 872	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40354 844 1779 9640	1.4% 1.7% 2.6% 3.4% 3.6% 4.0% 4.0% 4.0% 4.2% 4.4% 4.4% 4.4% 4.4% 4.5% 4.5% 4.5% 4.5% 4.7% 4.8% 4.8% 4.8%	1.83 [0.72, 4.83] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.83 [0.74, 0.94] 1.01 [0.94, 1.09] 0.84 [0.81, 0.88] 0.99 [0.95, 1.02]	
Tsusui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017 Coles 2014 Koh 2017 Cheng 2014	8 10 188 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 9 221 242 2512 242 2512	38 115 858 674 256 596 318 227 281 2210 265 460 2087 108 875 364 12819 15184 504 346 9019 5626	10 13 23 80 97 106 118 362 92 231 264 178 313 83 245 614 1142 1009 444 1227 3180 6727 7406	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40354 844 1779 9640 18897	1.7% 2.0% 2.6% 3.4% 3.6% 4.0% 4.0% 4.0% 4.1% 4.2% 4.4% 4.4% 4.4% 4.5% 4.5% 4.6% 4.5% 4.6% 4.7% 4.8% 4.8%	1.83 [0.72, 4.03] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.83 [0.74, 0.94] 1.01 [0.94, 1.09] 0.84 [0.81, 0.88] 0.99 [0.95, 1.03] 0.95 [0.54, 0.51] 0.95 [0.54, 0.55] 0.95 [0.55, 0	
Tsusui 2001 Delepaul 2017 Margolis 2017 Toma 2013 Lam 2018 Tsuji 2017 Hamatani 2017 Gomez-Otero 2016 Espartero 2017 Chioncel 2017 Bhambhani 2017 Bonsu 2017 Pascual-Figal 2017 Löfman 2017 Rickenbacher 2017 Choi 2017 Coles 2015 Kapoor 2016 Steinberg 2012 Farré 2017 Coles 2014 Koh 2017 Cheng 2014 Vedin 2017	8 10 18 23 30 41 60 55 56 168 63 89 128 163 70 171 157 333 349 128 2512 2512 2512 242 2512	38 115 858 674 256 596 318 227 281 2212 200 265 460 2087 108 875 364 12819 15184 504 346 9019 5626 9025	10 13 23 80 97 106 118 366 92 231 264 178 313 83 245 614 1142 1009 444 1227 3180 6727 7100	109 1013 539 574 2057 614 610 1664 1462 811 878 635 3908 112 1357 1476 38056 40356 40356 40356 40356 40356 18897 9640 18897 9957	1.7% 2.6% 3.4% 3.6% 4.0% 4.0% 4.2% 4.2% 4.4% 4.4% 4.4% 4.5% 4.5% 4.5% 4.5% 4.5	1.83 [0.72, 4.03] 0.95 [0.41, 2.19] 1.63 [0.81, 3.32] 0.80 [0.45, 1.41] 0.84 [0.57, 1.25] 1.46 [1.02, 2.08] 1.09 [0.82, 1.46] 1.25 [0.95, 1.66] 0.91 [0.70, 1.16] 1.21 [0.94, 1.54] 1.11 [0.88, 1.39] 1.12 [0.92, 1.36] 0.99 [0.82, 1.20] 0.98 [0.81, 1.17] 0.87 [0.73, 1.04] 1.08 [0.91, 1.29] 1.04 [0.91, 1.18] 0.87 [0.77, 0.98] 0.92 [0.82, 1.04] 0.83 [0.74, 0.94] 1.01 [0.94, 1.09] 0.84 [0.81, 0.88] 0.99 [0.95, 1.03] 0.53 [0.51, 0.54] 4.00 [0.91, 0.54]	
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Figure 2 Forest plots demonstrating all-cause death in (A) HFrEF and HFmrEF and (B) HFpEF and HFmrEF. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.

mortality, all-cause hospital re-admission, and HF-related hospital re-admission, so we pooled these outcomes to better understand this new entity of  ${\rm HF.}^2$ 

Our meta-analysis is the largest study meta-analysing the results of HFmrEF prognosis in the elderly population. Our study further supports the European Society of Cardiology Figure 3 Forest plots demonstrating (A, B) cardiac and (C, D) non-cardiac mortality rates. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.

	Ufmr	-r	UErE	r		Dick Datio	Dick Patio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Bonsu 2017	86	265	116	354	18.3%	0.99 [0.79, 1.25]	
Chioncel 2017	1119	2212	2921	5460	21.3%	0.95 [0.90, 0.99]	-
Hamatani 2017	26	318	101	860	13.8%	0.70 [0.46, 1.05]	
Pascual-Figal 2017	93	460	621	2351	19.1%	0.77 [0.63, 0.93]	
Steinberg 2012	20	674	57	730	11.8%	0.38 [0.23, 0.63]	(
Tsuji 2017	41	596	148	4474	15.7%	2.08 [1.49, 2.91]	
Total (95% CI)		4525		14229	100.0%	0.89 [0.69, 1.15]	◆
Total events	1385		3964				
Heterogeneity: Tau <sup>2</sup> = 0	0.08; Chi <sup>2</sup>	'= 41.1	5, df = 5 (	(P < 0.00)	0001); I² =	: 88%	
Test for overall effect: 2	2 = 0.88 (/	P= 0.38	8)				HFmrEF HFrEF
o	HFm	T	HFp	EF		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bonsu 2017	86	265	252	878	10.4%	1.13 [0.92, 1.38]	
Chioncel 2017	1119	2212	690	1462	13.1%	1.07 [1.00, 1.15]	
Hamatani 2017	26	318	42	614	2.5%	1.20 [0.75, 1.91]	
Pascual-Figal 2017	93	400	110	635	8.2%	1.17 [0.91, 1.50]	
Steinberg 2012	20	506	10	2146	1.0%	1.00 [0.52, 1.91]	
150/12017	41	290	90	2145	3.770	1.55[1.09, 2.21]	
Total (95% CI)		4525		6273	100.0%	1.11 [1.04, 1.18]	◆
Total events	1385		1205				
Heterogeneity: Chi* =	4.75, df =	5 (P=	0.45); 1*	= 0%			0.5 0.7 1 1.5
lest for overall effect:	Z = 3.18	(P=0.0	JU1)				HFmrEF HFpEF
	HFmr	EF	HFr	EF		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Tota	Weigh	t M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chioncel 2017	615	2212	1097	5460	72.6%	5 1.38 [1.27, 1.51]	
Farré 2017	72	504	265	2232	11.2%	5 1.20 [0.94, 1.53]	
Hamatani 2017	34	318	77	860	4.8%	1.19 [0.81, 1.75]	
Pascual-Figal 2017	35	460	155	2351	5.8%	1.15 [0.81, 1.64]	
Tsuji 2017	37	596	54	730	5.6%	0.84 [0.56, 1.26]	
Total (95% CI)		4090		11633	100.09	1.31 [1.22, 1.41]	•
Total events	793		1648				
Heterogeneity: Chi <sup>2</sup> =	7.43, df=	4 (P=	0.11); l² =	= 46%			0.5 0.7 1 1.5
Test for overall effect:	Z = 7.00 (	( <i>P</i> < 0.0	10001)				HFmrEF HFrEF C
	HFmr	EF	HFpE	F		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chioncel 2017	615	2212	449	1462	34.3%	0.91 [0.82, 1.00]	
Farré 2017	72	504	163	844	22.2%	0.74 [0.57, 0.95]	
Hamatani 2017	34	318	64	614	14.0%	1.03 [0.69, 1.52]	
Pascual-Figal 2017	35	460	68	635	14.2%	0.71 [0.48, 1.05]	
Tsuji 2017	37	596	97	2154	15.3%	1.38 [0.95, 1.99]	+
Total (95% CI)		4090		5709	100.0%	0.91 [0.75, 1.09]	
Total events	702		841	00.00000			-
Heteroneneity Tau?-	0.02.00	= 0 20	) df = 4 //	P= 0.05	) IZ = 570	6	
Test for overall effect:	7=1.02/	P= 0.30	n)	- 0.00	1 - 577	×	0.5 0.7 1 1.5 2
restion overall effect. 2	- 1.03 (	, = 0.3	~				HFmrEF HFpEF

guidelines by showing a significant difference between HFmrEF and HFrEF or HFpEF. This further supports the guidelines considering HFmrEF as a separate entity. Our metaanalysis detected a significant difference between HFrEF and HFmrEF regarding all-cause death and non-cardiac death, but there was no difference between the two arms regarding cardiac mortality, all-cause hospitalization, or HF-related hospitalization. On the other hand, we detected a significant difference between HFpEF and HFmrEF regarding cardiac mortality, but there was no significant difference between the two arms regarding all-cause death, non-cardiac mortality, all-cause hospitalization, or HF-related hospitalization.

These findings further support the statistical evidence making it a separate entity, but the clinical significance of HFmrEF separation must be reconsidered as only few of the outcomes significantly differed between the HF subtypes,

HFmrEF HFrEF **Risk Ratio Risk Ratio** Study or Subgroup **Events Total Events** Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 2212 14576 Chioncel 2017 487 18398 25.1% 0.28 (0.26, 0.30) Shah 2017 2716 3285 1742 5460 25.1% 2.59 [2.49, 2.70] Toma 2013 1.17 [0.95, 1.44] 92 674 523 4474 25.1% Tsutsui 2001 15 38 24.7% 0.80 [0.51, 1.26] 36 73 Total (95% CI) 28405 100.0% 0.91 [0.18, 4.59] 6209 16877 Total events 3310 Heterogeneity: Tau<sup>2</sup> = 2.72; Chi<sup>2</sup> = 3107.81, df = 3 (P < 0.00001); l<sup>2</sup> = 100% 0.002 0.1 10 Test for overall effect: Z = 0.12 (P = 0.91) Α HFmrEF HFrEF HFmrEF HFDEF **Risk Ratio Risk Ratio** M-H, Random, 95% CI Study or Subgroup **Events Total Events** Total Weight M-H, Random, 95% CI Chioncel 2017 487 2212 32.4% 0.94 [0.83, 1.06] 344 1462 Shah 2017 2716 3285 14892 18299 48.1% 1.02 [1.00, 1.03] Toma 2013 98 14.6% 0.75 [0.58, 0.97] 92 674 539 Tsutsui 2001 15 38 23 61 4.9% 1.05 [0.63, 1.74] Total (95% CI) 6209 20361 100.0% 0.95 [0.84, 1.07] 15357 Total events 3310 Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 7.97, df = 3 (P = 0.05); l<sup>2</sup> = 62% 0.5 0.7 1.5 Test for overall effect: Z = 0.88 (P = 0.38) B HFmrEF HFpEF HFmrEF HFrEF **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Cheng 2014 2340 5626 6664 15716 19.4% 0.98 (0.95, 1.02) Chioncel 2017 192 2212 797 5460 13.2% 0.59 [0.51, 0.69] Farré 2017 157 504 724 2232 13.6% 0.96 [0.83, 1.11] Gomez-Otero 2016 67 227 178 8.9% 0.97 (0.76, 1.22) 583 Hamatani 2017 85 318 238 860 9.9% 0.97 [0.78, 1.19] Lam 2018 73 256 289 1209 9.6% 1.19 [0.96, 1.48] Shah 2017 1416 3285 8505 18398 19.2% 0.93/0.89/0.971 Toma 2013 42 674 286 4474 6.2% 0.97 [0.71, 1.33] Total (95% CI) 48932 100.0% 0.92 [0.84, 1.01] 13102 17681 Total events 4372 Heterogeneity: Tau<sup>2</sup> = 0.01; Chi<sup>2</sup> = 46.26, df = 7 (P < 0.00001); I<sup>2</sup> = 85% 0.5 0'7 1.5 Test for overall effect: Z = 1.72 (P = 0.08) С HEMIEE HEIEE HFmrEF HFDEF **Risk Ratio Risk Ratio** Total Weight M-H, Random, 95% Cl Study or Subgroup **Events** Total **Events** M-H. Random, 95% CI Cheng 2014 2340 5626 4592 18897 13.8% 1.71 [1.64, 1.78] Chioncel 2017 192 2212 142 1462 12.6% 0.89 (0.73. 1.10) Farré 2017 157 504 378 844 13.2% 0.70 [0.60, 0.81] Gomez-Otero 2016 67 227 182 610 12.3% 0.99 [0.78, 1.25] Hamatani 2017 85 318 154 614 12.3% 1.07 [0.85, 1.34] Lam 2018 73 256 119 574 12.1% 1.38 [1.07, 1.77] 1.12 [1.07, 1.16] Shah 2017 1416 3285 7072 18299 13.8% Toma 2013 42 674 43 539 9.9% 0.78 [0.52, 1.18] Total (95% CI) 41839 100.0% 13102 1.05 [0.83, 1.33] Total events 4372 12682 Heterogeneity: Tau<sup>2</sup> = 0.11; Chi<sup>2</sup> = 319.28, df = 7 (P < 0.00001); l<sup>2</sup> = 98% 0.2 0.5 Test for overall effect: Z = 0.39 (P = 0.69) D HFmrEF HFpEF

Figure 4 Forest plots demonstrating (A, B) all-cause hospitalization and (C, D) HF-related hospitalization. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.

and the measures of those outcomes did not show a high clinical significance.

Accordingly, we recommend developing other studies evaluating the cut-off points separating the HF subtypes. Future studies should consider the transition or the change of HF status over time as this may affect the outcomes. This could help prevent data overlap between the HF subtypes. Also, they should consider other factors affecting the outcomes such as distinguishing between acute and chronic HF and the data distribution inside each arm of HF.

Our study was limited by the marked level of heterogeneity across the studies, the different distribution of precipitating factors of HF possibly playing as confounders, the probably misleading values of RRs (which do not consider the different periods of follow-up), the type of HF (either acute or chronic), and the similarity in the outcome between the three HF subtypes, but this may be explained as the eligible patients in some of the included studies belonged to the same medical centre and were of the same race, which raises the suspicion that their similar lifestyle and co-morbidities are the reason why they have similar mortality rates rather than being influenced by the subtype of HF they have. Also, 20 studies were eligible. Not all of them discussed the four outcomes as primary endpoints, so the small number of the data points made the outcome analysis less informative.

# Conclusions

In conclusion, significant differences of hospitalization and mortality were detected between HFmrEF and the other subtypes of HF, which supports classifying HFmrEF as a special subtype.

# **Conflict of interest**

None declared.

# References

- Lam CSP, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). *Eur J Heart Fail* 2014; 16: 1049–1055.
- 2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH van der MP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Hear Fail 2016; 18: 891-975.
- Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; **126**: 65–75.
- McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P,

Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail* 2012; **14**: 803–869.

- He K-L, Burkhoff D, Leng W-X, Liang Z-R, Fan L, Wang J, Maurer MS. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. *Am J Cardiol* 2009; 103: 845–851.
- Solomon SD, Anavekar N, Skali H, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**: 3738–3744.
- Gottdiener JS, Mcclelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002; 137: 631–640.
- Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, Pfisterer M, Brunner-la Rocca HP; TIME-CHF Investigators. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017; 19: 1586–1596.
- 9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009; **151**: 264–269.

- U.S. Department of Health & Human Services N. Study Quality Assessment Tools [Internet]. https://www.nhlbi. nih.gov/health-topics/study-qualityassessment-tools
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
- 12. Gomez-Otero I, Ferrero-Gregori A, Varela Roman A, Seijas Amigo J, Pascual-Figal DA, Delgado Jimenez J, Álvarez-García J, Fernández-Avilés F, Worner Diz F, Alonso-Pulpón L, Cinca J, Gónzalez-Juanatey JR. Mid-range ejection fraction does not permit risk stratification among patients hospitalized for heart failure. *Rev Esp Cardiol* (*Engl Ed*) 2017; **70**: 338–346.
- Margolis G, Khoury S, Ben-Shoshan J, Letourneau-Shesaf S, Flint N, Keren G, Shacham Y. Prognostic implications of mid-range left ventricular ejection fraction on patients presenting with STsegment elevation myocardial infarction. *Am J Cardiol* 2017; **120**: 186–190.
- Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Darling CE, Goldberg RJ. Magnitude of and prognostic factors associated with 1-year mortality after hospital discharge for acute decompensated heart failure based on ejection fraction findings. J Am Hear Assoc Cardiovasc Cerebrovasc Dis 2015; 4: e002303.
- Coles AH, Fisher K, Darling C, Yarzebski J, McManus DD, Gore JM, Lessard D, Goldberg RJ. Long-term survival for patients with acute decompensated heart failure according to ejection fraction findings. *Am J Cardiol* 2014; 114: 862–868.
- Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017; 70: 2476–2486.
- 17. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P,

Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.

- 18. Guisado-Espartero ME, Salamanca-Bautista P, Aramburu-Bodas O, Conde-Martel A, Arias-Jimenez JL, Llacer-Iborra P, Dávila-Ramos MF, Cabanes-Hernández Y, Manzano L, Montero-Pérez-Barquero M. Heart failure with mid-range ejection fraction in patients admitted to internal medicine departments: findings from the RICA Registry. Int J Cardiol 2018; 255: 124–128.
- 19. Farré N, Lupon J, Roig E. Gonzalez-Costello J, Vila J, Perez S, de Antonio M, Solé-González E, Sánchez-Enrique C, Moliner P, Ruiz S, Enjuanes C, Mirabet S, Bayes-Genis A, Comín-Colet J. Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: a multicentre prospective observational study in Catalonia (Spain). BMJ Open 2017; 7: e018719.
- 20. Bhambhani V, Kizer JR, Lima JAC, van der Harst P, Bahrami H, Nayor M, de Filippi CR, Enserro D, Blaha MJ, Cushman M, Wang TJ, Gansevoort RT, Fox CS, Gaggin HK, Kop WJ, Liu K, Vasan RS, Psaty BM, Lee DS, Brouwers FP, Hillege HL, Bartz TM, Benjamin EJ, Chan C, Allison M, Gardin JM, Januzzi JL Jr, Levy D, Herrington DM, van Gilst WH, Bertoni AG, Larson MG, de Boer RA, Gottdiener JS, Shah SJ, Ho JE. Predictors and outcomes of heart failure with mid-range ejection fraction. Eur J Heart Fail 2018; 20: 651–659.
- 21. Choi KH, Lee GY, Choi J-O, Jeon E-S, Lee H-Y, Cho H-J, Lee SE, Kim MS, Kim JJ, Hwang KK, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Park HY, Cho MC, Oh BH. Outcomes of de novo and acute decompensated heart failure patients according to ejection fraction. *Heart* 2018; **104**: 525–532.
- 22. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OÖ, Savarese G, Dahlström U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved,

midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017; **10**: e003875.

- Bonsu KO, Owusu IK, Buabeng KO, Reidpath DD, Kadirvelu A. Clinical characteristics and prognosis of patients admitted for heart failure: a 5-year retrospective study of African patients. *Int J Cardiol* 2017; 238: 128–135.
- 24. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634.
- 25. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, Roger-Rollé A, Domain G, Delon C, Uzan C, Boudjellil R, Carrié D, Roncalli J, Galinier M, Lairez O. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? ESC Hear Fail 2017; 4: 99–104.
- 26. Hamatani Y, Nagai T, Shiraishi Y, Kohsaka S, Nakai M, Nishimura K, Kohno T, Nagatomo Y, Asaumi Y, Goda A, Mizuno A, Yasuda S, Ogawa H, Yoshikawa T, Anzai T, Investigators for the WET-NaDEF Collaboration Project. Long-term prognostic significance of plasma B-type natriuretic peptide level in patients with acute heart failure with reduced, mid-range, and preserved ejection fractions. *Am J Cardiol* 2018; **121**: 731–738.
- 27. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Mark Richards A, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J* 2018; **39**: 1770–1780.
- Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, Vazquez R, Delgado-Jimenez J, Alvarez-Garcia J, Gimeno-Blanes JR, Worner-Diz F, Bardají A, Alonso-Pulpon L, Gonzalez-Juanatey JR, Cinca J, MUSIC and REDINSCOR I research groups. Mid-range left ventricular ejection fraction: clinical profile and cause of death in ambulatory patients with chronic heart failure. *Int J Cardiol* 2017; 240: 265–270.
- 29. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Outcomes in patients with heart failure with preserved, borderline,

and reduced ejection fraction in the Medicare population. *Am Heart J* 2014; **168**: 721–730.

- 30. Toma M, Ezekowitz JA, Bakal JA, O'Connor CM, Hernandez AF, Sardar MR, Zolty R, Massie BM, Swedberg K, Armstrong PW, Starling RC. The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insights from the ASCEND-HF Trial. Eur J Heart Fail 2014; 16: 334–341.
- 31. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail 2016; 4: 464–472.
- 32. Löfman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail* 2017; **19**: 1606–1614.
- Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol* 2001; 88: 530–533.
- 34. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi J, Miyata S, Shimokawa H, on behalf of the CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART-2 Study. Eur J Heart Fail 2017; 19: 1258–1269.
- 35. Gómez-Otero I, Ferrero-Gregori A, Varela Román A, Seijas Amigo J, Pascual-Figal DA, Delgado Jiménez J, Álvarez-García J, Fernández-Avilés F, Worner Diz F, Alonso-Pulpón L, Cinca J, Gónzalez-Juanatey JR, Red Española de Insuficiencia Cardiaca researchers (REDINSCOR II). Mid-range ejection fraction does not permit risk stratification among patients hospitalized for heart failure. *Rev Esp Cardiol (Engl Ed)* 2017; **70**: 338–346.
- Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011; 32: 670–679.